ACUTE TOXICITY SUMMARY

1,4-DIOXANE

(diethylene oxide; p-dioxane; glycolethylene ether; tetrahydro-p-dioxin)

CAS Registry Number: 123-91-1

I. Acute Toxicity Summary (for a 1-hour exposure)

Inhalation reference exposure level	**3,000 μg/m³**
Critical effect(s)	Nasal and eye irritation in healthy human volunteers
Hazard Index target(s)	Respiratory System; Eyes

II. Physical and Chemical Properties (ACGIH, 1991 except as noted)

Description	colorless liquid
Molecular formula	$C_4H_8O_2$
Molecular weight	88.1
Density	1.0329 g/cm^3 @ 20°C
Boiling point	101.1°C @ 760 mm Hg
Melting point	11.8°C
Vapor pressure	29 mm Hg @ 20°C
Flash point	12.22°C (closed cup)
Explosive limits	2 - 22 % by volume in air
Solubility	soluble in water and most organic solvents
Odor threshold	24 ppm (ACGIH, 1991); 1.8 ppm (Hellman and Small, 1974)
Odor description	ethereal odor (Buffler *et al*., 1978)
Metabolites	hydroxyethoxyacetic acid (Braun and Young, 1977)
Conversion factor	1 ppm = 3.6 mg/m³

III. Major Uses or Sources

1,4 - Dioxane is used as a solvent for oils, resins, waxes, adhesives, cellulose esters and ethers. It is also used as a stabilizer in chlorinated solvents (ACGIH, 1991). As much as 90% of U.S. production of dioxane has been used to stabilize chlorinated solvents. As a stabilizer it is present as a few percent by volume.

IV. Acute Toxicity to Humans

There are case reports of lethal hemorrhagic nephritis in workers exposed to unspecified high concentrations of 1,4-dioxane for several days (Barber, 1934; Johnstone, 1959).

1,4-Dioxane was irritating to the eyes, nasal passages, and the throat of adult volunteers following a 10-minute exposure to 1,600 ppm (Yant *et al*., 1930). In this study, no control subjects were tested concomitantly. A similar study of 4-6 volunteers by Fairly *et al*. (1934) showed that inhalation exposure to a concentration of 1,000 ppm (3,600 mg/m³) for five minutes caused a warm sensation in the throat and chest, but no noticeable irritation. However, in a more recent study, four healthy adult male volunteers exposed in a chamber for 6 hours to 50 ppm (180 mg/m³) dioxane exhibited eye irritation and 2 of the 4 subjects reported olfactory fatigue after 4 and 5 hours (Young *et al*., 1977).

Predisposing Conditions for 1,4-Dioxane Toxicity

Medical: Persons with preexisting skin, eye, respiratory, neurological, and liver and kidney conditions might be more sensitive (Reprotext, 1999).

Chemical: Unknown

V. Acute Toxicity to Laboratory Animals

Inhalation by guinea pigs and rats of 10,000 ppm (36,000 mg/m³) 1,4-dioxane for two 1.5-hour exposures was lethal (Fairley *et al*., 1934). 1,4-Dioxane affects the rat central nervous system as measured by a significant decrease in avoidance behavior following a 4-hour exposure to 3,000 ppm (10,800 mg/m³) (Goldberg *et al*., 1964). Nasal irritation was indicated by behavioral signs in guinea pigs exposed to 1,000 ppm (3,600 mg/m³) 1,4-dioxane for 4 hours (Yant *et al*., 1930); behavioral signs of eye irritation were evident at concentrations of 2,000 ppm (7,200 mg/m³) 1,4-dioxane or greater. Slight hyperemia was observed in the lungs, large air passages, and the brain in the animals exhibiting mild irritation. No histological changes were noted in control animals (unexposed to 1,4-dioxane). The absence of pathological lesions in the brain and lungs in exposed animals 9-10 days after 1,4-dioxane exposure led the authors to conclude that the histological effects of dioxane exposure were transient at the concentrations and exposure duration tested.

Based on pharmacokinetic data, rats appear to be the most appropriate animal model for metabolism of 1,4-dioxane in humans (Young *et al*., 1978). In a comparative toxicity study on rats, mice, guinea pigs, and rabbits, Fairley *et al*. (1934) showed that all species became drowsy after a 1.5 hour exposure to 1,000 ppm (3,600 mg/m³) 1,4-dioxane. In this study, guinea pigs were the most sensitive species to organ-specific histopathological lesions, which included: acute vascular congestion in the lungs, patchy cell degeneration and hemorrhage of the renal cortex, and hepatic necrosis. Schrenk and Yant (1936) showed that nasal irritation was evident in guinea pigs immediately following brief exposure to 1,000 ppm (3,600 mg/m³) 1,4-dioxane. No behavior indicative of eye irritation or lacrimation was observed at this concentration.

Drew *et al*. (1978) showed that a single 4-hour inhalation of 1,000 ppm (3,600 mg/m³) 1,4-dioxane by rats resulted in immediate elevation of serum glutamic-oxaloacetic transaminase activity. Alanine aminotransferase and ornithine carbamyl transaminase activities were elevated

24 hours following the 4-hour 1,000 ppm (3,600 mg/m³) exposure. The elevations of these hepatic enzymes indicated that 1,4-dioxane is hepatotoxic in rats.

VI. Reproductive or Developmental Toxicity

Pregnant rats treated with 0, 0.25, 0.5, or 1.0 mL dioxane/kg body weight by gavage on days 6-15 of gestation showed no differences in the number of implanted fetuses, live fetuses, post-implantation loss, or major malformations. Slight maternal toxicity in the form of weight loss was observed at the 1.0 mL/kg dose (Giavini *et al*., 1985). No data on human reproductive toxicity were available.

VII. Derivation of Acute Reference Exposure Level and Other Severity Levels (for a 1-hour exposure)

Reference Exposure Level (protective against mild adverse effects): 0.8 ppm (3,000 µg/m³)

Study	Young *et al*., 1977
Study population	4 healthy human male volunteers
Exposure method	chamber
Critical effects	subjective reports of eye irritation
LOAEL	50 ppm
NOAEL	not reported
Exposure duration	6 hours
Extrapolation to 1 hour	not used (see below)
Extrapolated 1-hour concentration	50 ppm
LOAEL uncertainty factor	6 (mild irritation)
Interspecies uncertainty factor	1
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	60
Reference Exposure Level	0.8 ppm (3 mg/m³, 3,000 µg/m³)

The volunteers complained of eye irritation throughout the exposure. Two of the subjects were not able to perceive the odor of dioxane after 4 and 5 hours exposure, respectively. A time-adjustment factor for the 6-hour exposure was not used since the individuals complained of eye irritation throughout the exposure.

Level Protective Against Severe Adverse Effects

No recommendation is made due to the limitations of the database.

Level Protective Against Life-threatening Effects

No recommendation is made due to the limitations of the database.

NIOSH (1995) lists a (revised) IDLH for 1,4-dioxane of 500 ppm based on acute inhalation toxicity data in animals. NIOSH derived 30 minute LC_{50}s from several studies of cats, rats, mice and guinea pigs, then divided the lowest 30 minute LC_{50} by 10 to determine an IDLH for humans. NIOSH stated that no relevant human data were available for the IDLH estimation.

VII. References

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